CLAIMS

1. A macrocyclic compound of general formula I,

$$V\text{-}CR^1R^2\text{-}Ar\text{-}CR^3R^4\text{-}N(R^5)\text{-}(CR^6R^7)_x\text{-}R^8 \qquad (I)$$

wherein V is a cyclic polyamine moiety having a total of 9 to 24 members and from 2 to 6 optionally substituted amine nitrogens spaced by two or more optionally substituted carbon atoms from each other, and which may optionally comprise a fused aromatic or heteroaromatic ring;

R^1 to R^7 may be the same or different and are independently selected from hydrogen or straight, branched or cyclic C_{1-6} alkyl;

R^8 is a heterocyclic group, a substituted aromatic group, or a mercaptan group;

Ar is an aromatic or heteroaromatic ring each optionally substituted at single or multiple positions with electron-donating or withdrawing groups;

x is 1 or 2;

and the acid addition salts and metal complexes thereof.

2. The macrocyclic compound of claim 1, wherein V is a 14 to 20 membered fused or unfused ring system.

3. A compound of claim 2, which is:

N-[4-(1,7-Diazacyclotetradecanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine (AMD-Exp 1).

4. A compound of claim 2, which is:

N-[7-(4,10-Diazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine (AMD-Exp 2).

5. A macrocyclic compound of general formula I,

$$V\text{-}CR^1R^2\text{-}Ar\text{-}CR^3R^4\text{-}N(R^5)\text{-}(CR^6R^7)_x\text{-}R^8 \qquad (I)$$

wherein V is a cyclic polyamine moiety having a total of 9 to 24 members and from 3 to 6 optionally substituted amine nitrogens spaced by two or more optionally substituted carbon atoms from each other, and which may optionally comprise a fused aromatic or heteroaromatic ring;

R^1 to R^7 may be the same or different and are independently selected from hydrogen or straight, branched or cyclic C_{1-6} alkyl;

R^8 is a heterocyclic group, a substituted aromatic group, or a mercaptan group;

Ar is an aromatic or heteroaromatic ring each optionally substituted at single or multiple positions with electrons-donating or withdrawing groups;

x is 1 or 2;

and the acid addition salts and metal complexes thereof.

6. The macrocyclic compound of claim 5, wherein V is a 14 to 20 membered fused or unfused ring system.

7. The macrocyclic compound of claim 5, wherein V is a 4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl system or a 1,4,7-triazacyclotetra-decanyl or a 4,7,10-triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl system, or a 1,4,8,11-tetraazacyclotetradecanyl system or a derivative thereof.

8. A compound of claim 5, which is;

N-[4-(1,4,7-Triazacyclotetra-decanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine (AMD 7049);

N-[7-(4,7,10,17-Tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine (AMD 7050);

N-[7-(4,7,10-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine (AMD 7051);

N-[4-[4,7,10-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl]-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine (AMD 7058);

N-[1-(1,4,7-Triazacyclotetra-decanyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine (AMD 7059);

N-[4-[4,7,10,17-Tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl]-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine (AMD 7063);

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(amino-methyl)pyridine (AMD 3465);

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-*N*-methyl-2-(aminomethyl)pyridine (AMD 3538);

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-)amino-methyl)pyridine (AMD 3500);

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-3-(amino-methyl)pyridine (AMD 3499);

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-(2-amino-methyl-5-methyl)pyrazine (AMD 3498);

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(amino-ethyl)pyridine (AMD 3497);

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(amino-methyl)thoiphene (AMD 3516);

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-(amino-ethyl)mercaptan (AMD 3530);

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-2-amino-benzylamine (AMD 3517);

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-amino-benzylamine (AMD 3544);

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-(amino-ethyl)imidazole (AMD 3543); or

N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-benzylamine (AMD 3529);

N-[3-(3,6,17-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-

phenylenebis(methylene)]-2-(aminomethyl)pyridine (AMD 8630);
N-[3-(3,6,17-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,3-phenylenebis(methylene)]-2-(aminomethyl)pyridine (AMD8631);
N-[4-(4,7,17-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine (AMD7450);
N-[7-(4,7,17-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine (AMD7463);
N-[6-(3,6,9-Triazabicyclo[11.3.1]pentadeca-1(15),11, 13-trienyl)-1,3-phenylenebis(methylene)]-2-(aminomethyl)pyridine (AMD7097); or
N-[7-(4,10,17-Triazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl)-1,4-phenylenebis(methylene)]-2-(aminomethyl)pyridine (AMD-Exp 3); or
the acid addition salts and metal complexes thereof.

9. A macrocyclic compound of general formula V,

V^2-CR^9R^{10}-Ar^2 (V)

wherein V^2 is a cyclic polyamine moiety having a total of 9 to 24 members and from 3 to 6 optionally substituted amine nitrogens spaced by two or more optionally substituted carbon atoms from each other, and which may optionally comprise a fused aromatic or heteroaromatic ring;

R^9 and R^{10} may be the same or different and are independently selected from hydrogen or straight, branched or cyclic C_{1-6} alkyl;

Ar^2 is an aromatic or heterocyclic ring each optionally substituted at single or multiple positions with electron-donating or withdrawing groups and/or aromatic and heterocyclic groups and their alkyl derivatives thereof; and the acid addition salts and metal complexes.

10. The compound of claim 9, wherein V^2 is a cyclam or substituted cyclam system or a 1,4,8,11-tetraazacyclotetradecanyl system or a 4,7,10,17-tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-trienyl system.

11. The compound of claim 10, wherein Ar^2 is a heterocyclic or substituted heterocyclic.

12. The compound of claim 11, wherein the or heterocyclic substituents are independently selected from the group consisting of: alkoxy; alkyl; halogen and hydrogen.

13. The compound of claim 12, which is:
1-[2,6-Dimethoxypyrid-4-yl(methylene)]-1,4,8,11-tetraazacyclotetradecane (AMD 7032);
1-[2-Chloropyrid-4-yl(methylene)]-1,4,8,11-tetraazacyclotetradecane (AMD 7048);
1-[2,6-Dimethylpyrid-4-yl(methylene)]-1,4,8,11-tetraazacyclotetradecane (AMD 7060);
1-[2-Methylpyrid-4-yl(methylene)]-1,4,8,11-tetraazacyclotetradecane (AMD 7061);
1-[2,6-Dichloropyrid-4-yl(methylene)]-1,4,8,11-tetraazacyclotetradecane (AMD 3451); or
1-[2-Chloropyrid-5-yl(methylene)]-1,4,8,11-tetraazacyclotetradecane (AMD 3454); or
the acid addition salts and metal complexes thereof.

14. The compound of claim 10, wherein Ar^2 is an aromatic or substituted aromatic ring.

15. The compound of claim 14, wherein the aromatic substituents are independently selected from the group consisting of: alkoxy; alkyl; halogen; hydrogen; aromatic; heterocyclic or substituted heterocyclic.

16. The compound of claim 15, which is:
N-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-purine (AMD 3472);
1-[1,4,8,11-Tetraazacyclotetradecanyl-1,4-phenylenebis(methylene)]-4-phenylpiperazine (AMD3526); or
7-[4-methylphenyl (methylene)]-4,7,10,17-Tetraazabicyclo[13.3.1]heptadeca-1(17),13,15-triene (AMD 3484).

17. A pharmaceutical composition comprising an effective therapeutic amount of the compound of any one of claims 1 to 16.

18. A composition according to claim 17, in unit dosage form.

19. The use of a composition of claim 17, in the manufacture of a medicament for the treatment of HIV- or FIV-infected patients.

20. The use of a compound of claim 17, in the manufacture of a medicament for the treatment of a disease by the regulation of endothelial cell function.

21. The use of a composition of claim 17, in the manufacture of a medicament for the treatment of a disease relating to vascularization of the gastrointestinal tract; haematopoiesis; or cerebellar development.

22. A method of treating a patient infected with HIV or FIV, by administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising the composition of claim 17 in a pharmaceutically acceptable carrier.

23. A method of treating a patient with a disease related to the regulation of endothelial cell function, by administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising the composition of claim 13 in a pharmaceutically acceptable carrier.

24. A method of treating a patient with a disease relating to vascularization of the gastrointestinal tract; haematopoiesis; or cerebellar development, by administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising the composition of claim 17 in a pharmaceutically acceptable carrier.

25. A method of treating a patient with a disease relating to basal leukocyte trafficking or the extravasation and tissue infiltration of leukocytes in response to inciting antigens, by administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising the composition of claim 17 in a pharmaceutically acceptable carrier.

amen. a3

26. A pharmaceutical composition useful for treatment of a patient comprising an effective therapeutic amount of the compound of any one of claims 1 to 16, wherein said compound effectively binds to a chemokine receptor.

27. A method of treating a patient, by administering to said patient a therapeutically effective amount of a pharmaceutical composition comprising the composition of claim 17 in a pharmaceutically acceptable carrier, wherein said compound effectively binds to a chemokine receptor.

28. A pharmaceutical composition comprising a therapeutically effective amount of a compound of general formula I,

$$V\text{-}CR^1R^2\text{-}Ar\text{-}CR^3R^4\text{-}N(R^5)\text{-}(CR^6R^7)_x\text{-}R^8 \qquad (I)$$

wherein V is a cyclic polyamine moiety having a total of 9 to 24 members and from 2 to 6 optionally substituted amine nitrogens spaced by two or more optionally substituted carbon atoms from each other, and which may optionally comprise a fused aromatic or heteroaromatic ring;

R^1 to R^7 may be the same or different and are independently selected from hydrogen or straight, branched or cyclic C_{1-6} alkyl;

R^8 is a heterocyclic group, a substituted aromatic group, or a mercaptan group;

Ar is an aromatic or heteroaromatic ring each optionally substituted at single or multiple positions with electrons-donating or withdrawing groups;

x is 1 or 2;

and the acid addition salts and metal complexes thereof, and

wherein said pharmaceutical composition is useful for the treatment of inflammatory disease; cancer; central nervous system developmental disease; HIV; FIV; vasculature development disease; haematopoiesis and other chemokine mediated diseases or disorders.

29. A pharmaceutical composition comprising a therapeutically effective amount of a compound of general formula I,

$$V\text{-}CR^1R^2\text{-}Ar\text{-}CR^3R^4\text{-}N(R^5)\text{-}(CR^6R^7)_x\text{-}R^8 \qquad (I)$$

wherein V is a cyclic polyamine moiety having a total of 9 to 24 members and from 3 to 6 optionally substituted amine nitrogens spaced by two or more optionally substituted carbon atoms from each other, and which may optionally comprise a fused aromatic or heteroaromatic ring;

R^1 to R^7 may be the same or different and are independently selected from hydrogen or straight, branched or cyclic C_{1-6} alkyl;

R^8 is a heterocyclic group, a substituted aromatic group, or a mercaptan group;

Ar is an aromatic or heteroaromatic ring each optionally substituted at single or multiple positions with electrons-donating or withdrawing groups;

x is 1 or 2;

and the acid addition salts and metal complexes thereof, and

wherein said pharmaceutical composition is useful for the treatment of inflammatory disease; cancer; central nervous system developmental disease; HIV; FIV; vasculature development disease; haematopoiesis and other chemokine mediated diseases or disorders.

30. A pharmaceutical composition comprising a therapeutically effective amount of a compound of general formula V,

$$V^2\text{-}CR^9R^{10}\text{-}Ar^2 \qquad (V)$$

wherein V^2 is a cyclic polyamine moiety having a total of 9 to 24 members and from 3 to 6 optionally substituted amine nitrogens spaced by two or more optionally substituted carbon atoms from each other, and which may optionally comprise a fused aromatic or heteroaromatic ring;

R^9 and R^{10} may be the same or different and are independently selected from hydrogen or straight, branched or cyclic C_{1-6} alkyl;

Ar^2 is an aromatic or heterocyclic ring each optionally substituted at single or multiple positions with electron-donating or withdrawing groups and/or aromatic and heterocyclic groups and their alkyl derivatives thereof; and the acid addition salts and metal complexes, and

wherein said pharmaceutical composition is useful for the treatment of inflammatory disease; cancer; central nervous system developmental disease; HIV; FIV; vasculature development disease; haematopoiesis and other chemokine mediated diseases or disorders.

31. A pharmaceutical composition comprising a therapeutically effective amount of a compound of: AMD 3100 ((1,1'-[1,4-phenylenebis(methylene))]bis-1,4,8,11-tetraazacyclotetradecane), wherein said pharmaceutical composition is useful for the treatment of inflammatory disease; organ transplant rejection; cancer; central nervous system developmental disease; HIV; FIV; vasculature development disease; cardiogenesis developmental disease; haematopoiesis and other chemokine mediated diseases or disorders.

32. The pharmaceutical composition of claim 28, 29, 30 or 31, wherein said disease is arthritis.

33. The pharmaceutical composition of claim 28, 29, 30 or 31, wherein said disease is multiple sclerosis.

34. The pharmaceutical composition of claim 28, 29, 30 or 31, wherein said cancer is associated with: solid tumors; lymphoma; metastatic tumors; glioblastoma tumors; and other carcinoma tumors.

35. The pharmaceutical composition of claim 34, wherein said cancer is; non-small cell lung cancer; lung cancer; breast cancer; prostate cancer; and cancer of other organs.

36. A pharmaceutical composition of claim 28, 29, 30 or 31, wherein said disorder is treated by inhibiting or promoting angiogenesis or by inducing stasis of angiogenesis.

37. A method for the treatment of a patient comprising, administering a therapeutically effective dosage of the pharmaceutical composition of claim 28, 29, 30 or 31, to a patient with a disease or disorder that responds to said treatment over a period of time sufficient to effectively treat said disease or disorder.

38. A method for the prevention of a disease or disorder in a patient comprising, administering a therapeutically effective dosage of the pharmaceutical composition of claim 28, 29, 30 or 31, to a patient over a period of time sufficient to effectively prevent said disease or disorder.

add B2

add C4